VIENNESE SEROLOGICAL RESEARCH ABOUT THE YEAR 1900: ITS CONTRIBUTION TO THE DEVELOPMENT OF CLINICAL MEDICINE

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It is true that immunological discoveries of the Vienna School, such as agglutination (1896), precipitation (1897), and blood groups (1900), as well as the final definition of the concept of allergy (1906), are mentioned in every medical textbook. However, they are registered there only as firsts and the dates are given. Thus far no one has tried to consider them as a unified complex or to draw attention to the fact that the creative impulses for all these discoveries came from the same background. What I want to attempt, therefore, is to treat these discoveries, which concern some of the most basic laws of immunology, in their genetic affiliation. Such an undertaking must necessarily involve something else. We must attempt to study the facilities offered for experimental research in clinical medicine at that time, using serology—then one of the most promising medical fields—as our case in point. As we have chosen one of the leading medical centers for our discussion we may expect exemplary results.

W. D. Foster[1] states that, in general, hospital laboratories did not come into existence before the end of the 19th century. At the center of clinical university medicine, the General Hospital of Vienna, laboratories were still rudimentary. The clinic of Professor Hermann Nothnagel, for example, had one scantily equipped laboratory room at its disposal, where routine analyses of urine and blood could be carried out. What went beyond that, in particular the reception and further development of new ideas in medical research, fell to the theoretical institutes in the School of Medicine. These, it is true, were equipped poorly enough. Everything depended on the inventiveness of the heads of the various theoretical institutes and on their ability to improvise and to secure the cooperation of the clinics.

Against this background the pioneer work of Max Gruber (1853-1927)[2] must be evaluated. Beginning in 1887, he carried on his research in the four poorly equipped rooms of the Vienna Institute of Hygiene. But the problems which he attacked there were so timely that he also attracted pupils from abroad. Among them was Herbert E. Durham (1866-1945)[3] of Guy's Hospital, London. Thus the Vienna Institute of Hygiene not only became seminal for Viennese serological research but, through the activities of Durham, also determined the work done in this field in London. Further, we owe the prototype of all serodiagnostic test methods, the agglutination test, to the joint efforts of Austrian and British scientists. This is not the place, however, to go into greater detail concerning the history of that discovery.[4] In our context it is of interest only insofar as it influenced clinical practice and as it helped to develop further serodiagnostic methods.

Concerning both, it is interesting to note, first, that as early as January or February 1896, Durham and Gruber discovered the double applicability of the agglutination test: that it can be used both to identify bacteria and to detect specific agglutinin in blood serum. In March 1896 Gruber sent another pupil to the clinic of Professor Nothnagel, to look for typhoid agglutinins in the serum of patients. The fact that this pupil of Gruber, whose name was Albert Sidney Grünbaum, also came from London is another evidence of the close connections that existed between Vienna and London.

Gruber also did something else. He attended the annual meeting of internists at Wiesbaden, and on April 9, 1896, he informed the assembled physicians about the possibility of early diagnosis of typhoid fever and cholera by means of the agglutination test.[5] In spite of these early contacts with the clinicians, Gruber and his English pupils nevertheless must share their priority rights in this respect with the Frenchman F. J. Widal (1862-1929). The two cases of typhoid fever at Nothnagel's clinic in the spring of 1896 offered too small a basis for publication. Paris furnished more typhoid cases and then, on April 15, the discoveries of Gruber and Durham were made public there in the *Semaine médicale*. Widal's publication on the clinical utilization of serodiagnosis in typhoid could therefore appear as early as June 26.

The agglutination test very soon entered the clinics as a routine test.[6] As early as August 1897 Widal was able to report at the 65th annual meeting of the British Medical Association in Montreal that there

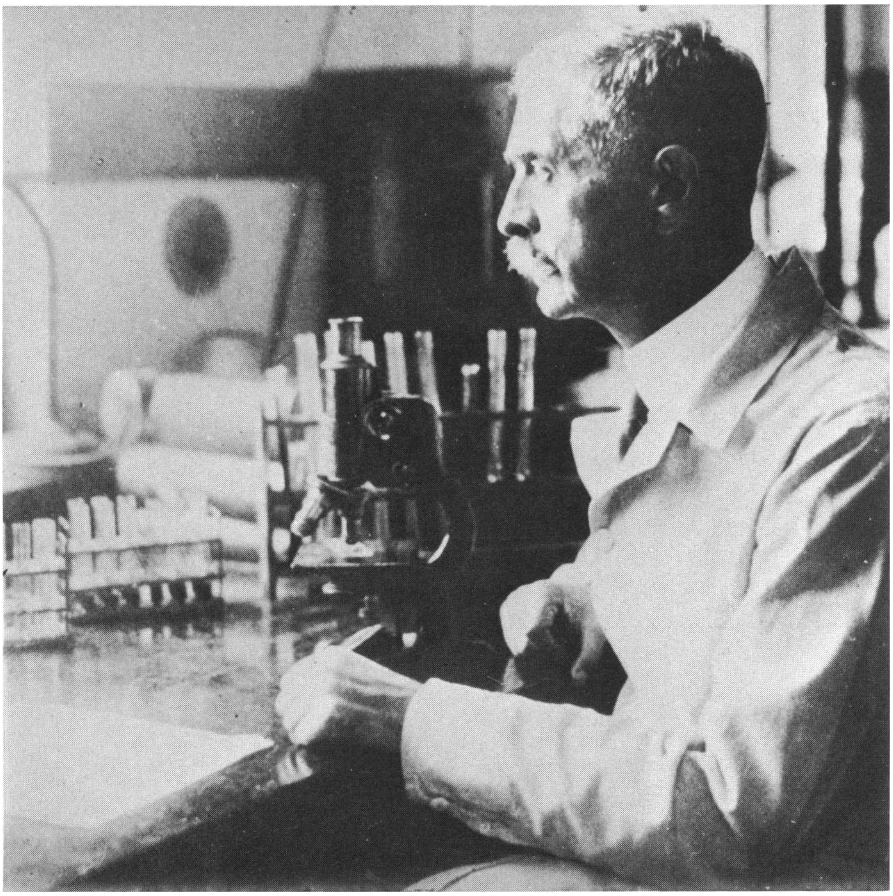

Fig. 1. Karl Landsteiner (1868-1943). All illustrations in this essay are based on original pictures in the archives of the Institute of the History of Medicine in Vienna.

were records of the test being done in several thousand cases.

While in 1896 the agglutination test, which later came to be called the Gruber-Widal test, began its triumphant advance through the clinics, its birthplace, the Institute of Hygiene in Vienna, witnessed preliminary experiments leading to another discovery of far-reaching importance. A young physician had entered the institute on January 1, 1896, as an assistant. He had previously concerned himself with chemical work alone, but in the new milieu he began to try his hand at serological experiments. This physician was Karl Landsteiner (1868-

1943),[7] (Figure 1) and we in no way undervalue his genius when we draw attention to the immediate connection between these discoveries. The discovery of the interagglutination of human sera, i.e., Landsteiner's theory of the human blood groups, was an outgrowth of Gruber's line of research and is based on the phenomenon of agglutination discovered by him and Durham. In 1900, when Landsteiner published his discovery of isoagglutination as a physiological phenomenon, he no longer was a member of the Institute of Hygiene. We are ignorant of the causes that made him give up a paid assistantship at the Institute of Hygiene to become an unsalaried volunteer at the Institute of Pathological Anatomy, which was headed by Anton Weichselbaum (1845-1920), the well-known discoverer of the *Diplococcus meningitidis*. We know, however, that the latter institute at the time of Landsteiner's transfer (1897) prided itself on a bacteriological laboratory that was well equipped according to the standards of the time. During the next 10 years (1897-1907), while Landsteiner worked there, this laboratory became a world-famous serological center. Landsteiner succeeded in interesting his colleagues at the Nothnagel clinic in his serological research. To what extent they took an active part in it is apparent from the famous publication on the blood groups (1901).[8] Two of Nothnagel's assistants mentioned there by Landsteiner, Alfred von Decastello-Rechtwehr (1872-1960) and Adriano Sturli, themselves defined the "no-type" AB blood group a year later. Julius Donath (1870-1919), with whom Landsteiner in 1904 clarified the pathophysiological mechanism of paroxysmal cold hemoglobinuria,[9] likewise came from the Northnagel clinic. Two years earlier, Landsteiner had cooperated with Josef Halban (1870-1937), who then was assistant at the First Gynaecological Clinic, in a study on immunity in the newborn.[10] In 1905-1906 Landsteiner, in cooperation with the venereologist Ernst Finger (1856-1939), succeeded in infecting monkeys with syphilis.[11] In 1907, together with Finger's assistant, Rudolf Müller (1877-1934), he explained the principle underlying the Wassermann reaction. These are some of the outstanding results which made Landsteiner's laboratory—in spite of its minimal size and utter simplicity of equipment, which seems almost incredible today—a center of immunological research connected with the Allgemeines Krankenhaus.

Before dealing with the third center of serological research in Vienna at the turn of the century, we must glance at the two other capitals of European medicine, Paris and Berlin, and inquire about the homes of

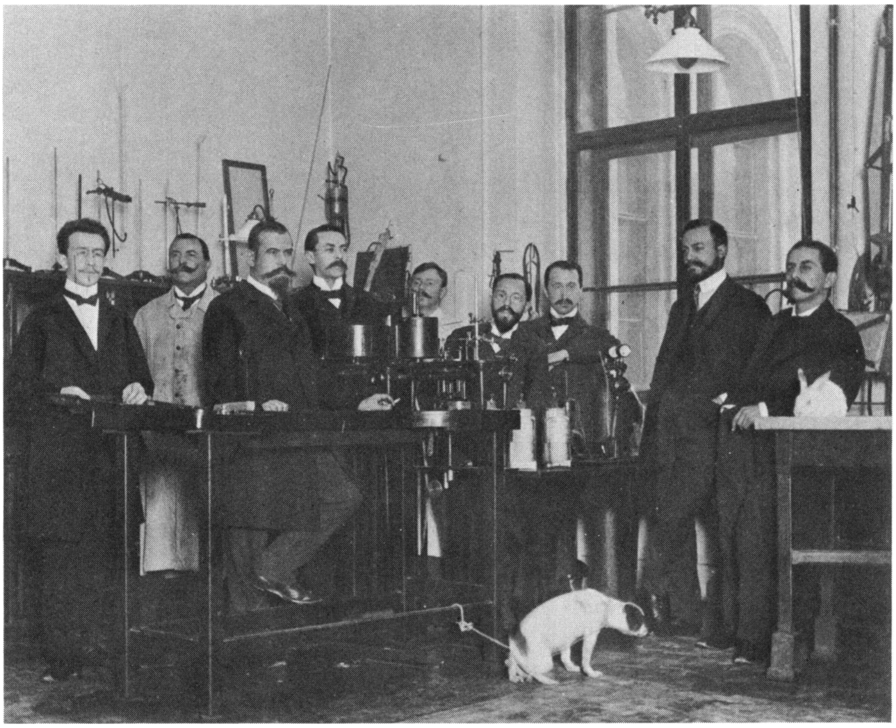

Fig. 2. Richard Paltauf (1858-1924) and his collaborators at the Institute of Experimental Pathology, Vienna. Photograph, 1905.

bacteriological and serological research there. We immediately think of the Institut Pasteur in Paris and the Institute for Infectious Diseases in Berlin, which was headed by Koch. In 1888 and 1891, respectively, the French nation and the German state had erected these institutes specifically for this new field, which proved equally important for therapy and prophylaxis; these institutes also had been equipped with the most modern facilities. We observe an essential difference. While this field of basic research received generous official support elsewhere, the Austrian pioneers Max Gruber and Karl Landsteiner were obliged to gain their results the hard way in laboratories in the Institute of Hygiene or the Institute of Pathological Anatomy that were improvised and possessed only modest means.

A change for the better finally came during the last years of the century. It is connected with the name of one man, Richard Paltauf (1858-1924)[12] (Figure 2). We cannot overestimate the fact that in 1894, when the therapeutic value of rabies antiserum and diphtheria serum could no longer be disregarded, a man appeared on the scene who founded a Rabies and Serotherapeutic Institute in Vienna. Paltauf's ultimate aim was the creation of a large research center with many departments, according to the Paris model. Paltauf was a pathological anatomist who, in 1893, became the head of the pathological anatomy department at the Rudolf Hospital. He proved to be a most successful large-scale organizer; from his skill not only this municipal hospital but also theoretical university medicine in general derived great benefit. Starting from the department of pathological anatomy in his home hospital, he built up in the course of a few years his "kingdom" of experimental medicine. This enterprise included the following institutions: the Rabies[13] and Serotherapeutic[14] Institute founded in 1894, the Serological Research Center of the department of pathological anatomy, the Histopathological Institute at the university and, since 1900, the Institute of General and Experimental Pathology.

In all these institutions Paltauf assembled a staff of gifted and even brilliant assistants. Among these we must mention first Rudolf Kraus (1868-1932)[15] and Robert Doerr (1871-1952);[16] the latter became professor of hygiene at Basel. These two men in turn attracted young clinicians not only from the Rudolf Hospital but also from the university clinics. Among those who worked at the serotherapeutic laboratory of the Rudolf Hospital were the pediatrician Clemens von Pirquet (1874-1929),[17] the surgeon Paul Clairmont, and the psychiatrists Wagner von Jauregg and Otto Pölzl—to mention only a few.

We see that a stage of serological research characterized by rapid development at the same time offered many powerful impulses to clinical therapy. In this connection I can give only a sketchy list of the most important of these influences. There is the discovery of the method of precipitation by Rudolf Kraus in 1897; this has become one of the indispensable routine tests in almost all fields of medicine.[18] There is the isolation of dysentery antitoxin, performed by Kraus in cooperation with Robert Doerr. This was followed by the production of antitoxic dysentery serum.[19] It was also in this group that, in the course of their search for useful sera, Ernst Lowenstein (1878-1949) and Michael Eisler-Terramare (1877-1970)[20] for the first time succeeded in preparing toxoids from tetanus toxin by means of formalin treatment. Eisler and Friedrich Silberstein put this tetanus toxoid to practical use in the production of tetanus serum, which became the model for Gaston Ramon (1886-1963) in the 1920s. Ramon produced diphtheria anatoxin in order to extract antitoxic immune sera and for the active immunization of humans.[21] As a last example I should like to mention gamma globulin. When this protein is used today hardly anyone remembers that we owe it to the biochemical pioneering work of Ernst Peter Pick (1872-1960).[22]

You will excuse this cursory enumeration, which serves merely to demonstrate the enormous scope of what was achieved under Paltauf. But I want to enlarge a little on a process which I can best characterize as a scientific chain reaction which seems especially apt to illustrate the interdependence of serological experiment and clinical diagnosis. I am thinking of Pirquet's conclusions about the nature of serum sickness (or the practice of vaccination) and the tuberculin test and their inclusion under the general concept of allergy.

Commentators[23] have rightly pointed to Pirquet's bold play of associations, which related far-off, long-known phenomena such as vaccination and newly found clinical phenomena (serum exanthema) to each other, and thus arrived at fundamental biological laws, such as the concept of allergy. Those who have been fascinated by the working of Pirquet's mind and have tried to follow his ideas have nevertheless neglected up to the present time to offer an adequate treatment of the laboratory foundations of his findings. Further, we must not fail to concentrate on the question of the part played by the serological laboratories of Paltauf and Rudolf Kraus in the immunological concepts of Pirquet (Figure 3).

In 1902 Rudolf Kraus, already famous as the discoverer of serological precipitation, published a study titled *Further Investigations Concerning Specific Precipitations*.[24] His collaborator was a young assistant in the pediatric clinic of the university, Clemens Pirquet. In this study Pirquet's own ideas are not yet apparent. He presents himself rather as an ardent pupil of Kraus, engaged in mastering Kraus' serological methods and concepts. The outward circumstances of this schooling were thus described by Pirquet's friend and colleague, Bela Schick (1877-

Fig. 3. Clemens von Pirquet (1874-1929). Unsigned etching.

1967):[25] "Immediately after lunch we all rushed by street car to the Serotherapeutisches Institut, where Paltauf and Rudolf Kraus worked. This institute was our laboratory. We had none in the clinic for several years."

In the same year, 1902, Paul Moser (1865-1924), first assistant at the pediatric clinic, came out with his scarlatinal antiserum.[26] Far from being an accidental coincidence, this achievement was evidence of the close cooperation that existed between the pediatric clinic and the Serotherapeutic Institute. The high dosages of Moser's serum that were used offered ample opportunities for Pirquet and Schick to study serum sickness, which they were the first to define as a separate syndrome.[27] Pirquet observed that when there was a second injection, the symptoms appeared at once or within a few hours, whereas after the first injection they took seven at 12 days to develop. This became the pivotal point for further considerations.[28]

With Pirquet putting the question about this reduction of the incubation period we have come to the mental processes which I have called a scientific chain reaction. Raising this question involves the raising of two further questions. These are Pirquet's very own: What is the nature of the incubation period, and what are the processes that induce the body to learn a different reaction: i.e., to acquire a new quality, for which Pirquet in 1906 devised the term allergy?[29] This is the crucial point in the statement of the problem. Here Pirquet the clinician most profitably became aware of everything Pirquet the serologist had learned from Kraus, the discoverer of serologic precipitation. The process of precipitation which he had so often observed in the test tube appeared to Pirquet to be a heuristic model. In the monograph on serum sickness,[30] which appeared in 1905, he explicitly refers to Kraus and his discovery. The reference occurs in the passage in which he expounds, at length and according to experiments, his hypothesis of the formation of precipitins to accord with his concept of serum sickness as an antigen-antibody reaction. When we read Pirquet's concluding remarks we find that the clinician has become one with the laboratory-centered serologist in an almost ideal way: "Just as the precipitate shows when we add one drop of horse serum to the serum containing antibody, the specific edema, the immediate reaction, occurs if an individual containing antibody is treated with horse serum."[31] The conclusion Pirquet draws from this analogy between the processes observed in the laboratory and in the clinic is contained in the following sentence in his book: "The reaction *in vivo* is as specific as that *in vitro*."[32]

This analogy was to be of the greatest consequence for clinical medicine. It suggested to Pirquet not only the explanation of the processes underlying revaccination, which had long been practiced, though its nature was not understood—Pirquet was able to explain it also as an antigen-antibody-reaction[33]—but also the tuberculin test that is known by his name.[34] If we for once consider this test in this way, the phenomena that appear in the skin become as plain as the phenomena that accompany serum sickness or revaccination. The characteristic reddening of the skin of persons infected with tuberculosis is caused by vaccination with tuberculin, just as the precipitate appears in the test tube filled with serum containing antibody when horse serum is added.

The tuberculin reaction was the crowning achievement of Pirquet's work. As this test dispenses with the test tube it represents the final transposition into the living body of the process observed in the test tube. A transformation of this kind could be achieved only by a scientist who, during his time in the laboratory, had also remained a true clinician.

Today the tuberculin test is performed all over the world. Apart from some modifications it has remained as conceived by Pirquet. Therefore we should not forget that, being an outgrowth of experiments conducted at the serological laboratory in Vienna, it offers one of the most impressive examples of the fertilizing influence of basic research on clinical medicine.

NOTES AND REFERENCES

1. Foster, W. D.: *A Short History of Clinical Pathology*. Edinburgh and London, Livingtone, 1961, p. 113.
2. Lesky, E.: *Die Wiener medizinische Schule im 19. Jahrhundert*. Graz-Köln, Böhlaus Nachf., 1965, p. 595 ff.
3. Foster, W. D., op. cit., p. 73 f.
4. On the history of agglutination see: Gruber, M.: Geschichte der Entdeckung der spezifischen Agglutination. In: *Handbuch der Immunitätsforschung und experimentellen Therapie*, Kraus, R. and Levaditi, C. editors. Jena, Lieferung, 1914, pp. 150-154. Reprinted under the title Agglutination in *Wien. Med. Wschr.* 77:742f, 1927. Paltauf, R.: Die Agglutination. In: *Handbuch d. pathog. Mikroorganismen*, Kolle, W. and Wassermann, A., editors. Jena, 1904, vol. 4, p. 645 ff. Bordet, J.: Geschichtlicher Überblick und allgemeine Anschauungen über Immunität. In: *Handbuch d. Immunitätsforschung und experimentellen Therapie*, Kraus, R. and Levaditi, editors. Jena, Lieferung, 1914, p. 43ff. Bulloch, W.: *The History of Bacteriology*. London, 1960, Oxford University Press, p. 266f.
5. Gruber, M.: Prioritätsanspruch. *Wien. Klin. Wschr.* 9:244, 1896.
6. Foster, W. D., op. cit., p. 76. By 1904 almost 1,000 scientific studies on agglutination had been published. Cf. Römer, P.: *Die Ehrlichsche Seitenket-*

tentheorie und ihre Bedeutung für die medizinische Wissenschaft. Wien, Hölder, 1904, p. 323.
7. Speiser, P.: *Karl Landsteiner.* Wien, 1961. Lesky, E., op. cit., p. 574. Simms, G. R.: *The scientific work of Karl Landsteiner.* Zürich, Med. Diss., 1965. Foster, W. D., op. cit., p. 107f. Schorr, M.: *Zur Geschichte der Bluttransfusion im 19. Jahrhundert.* Basel and Stuttgart, Basler Veröff. *Gesch. Med. Biol.,* Fasc. 7, 1956. Buess, H.: Der Ausbau der Blutttransfusion in neuester Zeit. *Bull. Schweiz. Akad. Med. Wiss. 9:*248-69, 1953.
8. Landsteiner, K.: Über Agglutinationserscheinungen normalen menschlichen Blutes. *Wien. Klin. Wschr. 14:*1132-34, 1901.
9. Donath, J. and Landsteiner, K..: Über paroxysmale Hämoglobinurie. *Münch. Med. Wschr. 51:*1590-93, 1904.
10. Halban, J. and Landsteiner, K.: Über Unterschiede des fötalen und mütterlichen Serums und über eine fällungshemmende Wirkung des Normalserums. *Münch. Med. Wschr. 49:*473-78, 1902.
11. Finger, E. and Landsteiner, K.: Untersuchungen über Syphilis an Affen. *Sitzb. Akad. Wiss. Wien.* 3, *114:*497-539, 1905; *115:*179-200, 1906; *Arch. Derm. Syph. 78:*335-68, 1906; *81:*147-66, 1906.
12. Lesky, E., op. cit., p. 577ff. Pick, E. P.: Richard Paltauf, seine Schule und ihre Forschungsergebnisse. *Wien. Klin. Wschr. 65,* 698-702, 1953.
13. Paltauf, R.: Die Errichtung der Anstalt zur Wuthschutzimpfung in der k.k. Krankenanstalt Rudolfsiftung. *Jahrb. Wien. Krank. 3:*912-29, 1894.
14. Paltauf, R.: Das staatliche Institut für Herstellung von Diphtherie Heilserum in Wien. Errichtung desselben und seine Tätigkeit im Jahre 1895. *Jahrb. Wien. Krank. 4:*1-52, 1895. Kraus, R.: Richard Paltauf und das Serotherapeutische Institut. *Wien. Med. Wschr. 77:*739-41, 1927. Teichmann, J.: *Bundesstaatliches Serotherapeutisches Institut Wien, 1894-1954.* Wien, Gruber, 1954.
15. Löwenstein, E. and Kraus, R. *Wien. Med. Wschr. 82:*1016f, 1932. Eisler, M.: *Wien. Klin. Wschr. 45:*1072f, 1932. Teichmann, J.: Zum 100. Geburtstag Rudolf Krans'. *Wien. Med Wschr. 118:* 869-72, 1968.
16. Reuter, F.: In memoriam R. Doerr. *Wien. Klin. Wschr. 64:*129f, 1952.
17. In this connection another two-man team should be mentioned. At the same time, in 1903, Pirquet had been connected with Max Gruber, who was already in Munich.
18. Kraus, R.: 30 Jahre Präzipitinlehre. *Wien. Med. Wschr. 77:*743f, 1927. Teichmann, J.: 70 Jahre Präzipitation. *Wien. Klin. Wschr. 79:*281-84, 1967.
19. Kraus, R. and Doerr, R.: Das Dysenterieserum. *Wien. Klin. Wschr. 19:*929f, 1906.
20. Teichmann, J.: Prof. Dr. M. Eisler-Terramare zum 80. Geburtstag. *Wien. Klin. Wschr. 69:*52f, 1957. Idem: Prof. Eisler-Terramare und sein Wirken am Serotherapeutischen Institut. *Mitt. Öst. Sanitäts-Verwaltung 58:*147-50, 1957.
21. Dagoquet, F.: L'immunité, histoire et méthode. *Conférence donnée au Palais de la Découverte.* D. 94. Paris o.J., 1964, p. 17 ff. Parish, H. J.: *A History of Immunization.* Edinburgh and London, Livingstone, 1965. p. 141f.
22. Pick, E. P.; *Wien, Klin. Wschr. 65:* 699, 1953; Brücke, F. T.: Ernst Peter Pick. Nachruf. *Alman. Öst. Akad. Wiss. 110:*446-59, 1960.
23. Wagner, R. *Clemens von Pirquet: His Life and Work.* Baltimore, Johns Hopkins Press, 1968, p. 16. Idem: Clemens von Pirquet, discoverer of the concept of allergy. *Bull. N.Y. Acad. Med. 40:*229-35, 1964.
24. *Centralblatt f. Bakteriologie, Parasitenkunde und Infectionskrankheiten 32:*60-74, 1902.
25. Schick, B.: Pediatrics in Vienna at the beginning of the century. *J. Ped. 50:* 119, 1957.
26. Schick, B. (op. cit., p. 119) speaks about the amazing results obtained with this serum. It becomes clear therefore that R. Kraus advocated calling the antitoxic scarlet fever antiserum according to Moser-Dick (Berechtigung, das antitoxische Scharlachserum Moser-Dick zu benennen. *Wien. Med. Wschr. 77:*745f,

1927) after the good results obtained with the Dick-Dochez serum in America became known. Cf. also Parish, H. J., op. cit., p. 198ff. Wagner, R., op. cit., p. 29.

27. This was in the monograph *Die Serumkrankheit,* Vienna, 1905, which he published with Bela Schick.
28. After Schick, B. (op. cit., p. 120) the first observation was made by Pirquet on December 2, 1902. Cf. von Pirquet, C. and Schick, B.: *Die Serumkrankheit.* Vienna, 1905, p. 77.
29. Pirquet, C. v.: Allergie. *Münch. Med. Wschr. 53:*1457-58, 1906. Idem: Zur Geschichte der Allergie. *Wien. Med. Wschr. 27:*745-48, 1927. Doerr, B.: Ueber Anaphylaxie. *Wien. Klin. Wschr. 27:*415-22, 1908. Idem: "Die Anaphylaxie." In: *Die Immunitätsforschung,* vol. 6. Wien, Springer, 1950. Idem: Die Allergie. Ibid., vol. 8. Wien, 1951. Blittersdorf, F.: Zur Geschichte der Serumkrankheit. *Sudhoffs Arch. Gesch. Med. 36:*149-58, 1943. Pache, H. D.: 50 Jahre Allergie in der Kinderheilkunde. *Münch. Med. Wschr. 98:*1233-36, 1956. Schadewaldt, H.: Die geschichtliche Bedeutung der Pädiatrie für die Entwicklung der Allergie. *Die Med.:* 14-15, 1959. Wagner, R., op. cit.[23] Parish, H. J., op. cit., p. 133.
30. Pirquet states that his coassistants, Hamburger and Moro, were the first to observe precipitation in the human body after an injection of horse serum. Pirquet, however, was not able to prove congruity between the concentration of precipitin and serum sickness either in humans or in rabbits. Pirquet therefore distinguished the antibodies causing serum sickness as "antibodies of vital reactions," different from the precipitins.
31. *Die Serumkrankheit,* p. 113f.
32. Pirquet, C.v.: *Klinische Studien über Vakzination und vakzinale Allergie.* Leipzig and Wien, 1907.
33. Following up these new lines of research, Pirquet even tried to explain the smallpox exanthem on the basis of agglutinins. How far he had now departed from the teachings of his original mentor becomes clear from the polemics into which Kraus entered against Pirquet in the Society of Physicans. Cf. Wagner, R., op. cit., p. 48.
34. First published under the title: Tuberkulindiagnose durch cutane Impfung. *Berl. Klin. Wschr. 44:*644f., 1907. Cf. *Wien. Med. Wschr. 57:*1369-1374, 1907; *Wien. Klin. Wschr. 20:*1123-28, 1907. Wagner, R., op. cit., p. 66.